Medizinische Poliklinik – Innenstadt

der Ludwig-Maximilians-Universität München

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Vergleich von Nominal- versus Hochdruckballoninflatation für optimale Koronarstent-Implantation durch IVUS und QCA mit EXPRESS™ Coronary Stent System

Dissertation

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...to my late father, who deserves all my love and affection

Glossary of Abbreviations

PCI	Percutaneous Coronary Intervention
IVUS	IntraVascular UltraSound
FFR	Fractional Flow Reserve
MLD	Minimum Lumen Diameter
CSA	Cross-Sectional Area
QCA	Quantitative Coronary Angiography
PTCA	Percutaneous Transluminal Coronary Angioplasty
MUSIC	Multicenter Ultrasound Stenting In Coronaries study
BENESTENT	BElgian NEtherlands STENT study
LAD	Left Anterior Descending coronary artery
LCX	Left Circumflex coronary artery
RCA	Right Coronary Artery
SAM	Surface-Adherent Monocytes
TIM	Tissue-Infiltrating Monocytes

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1. INTRODUCTION

1.2 Coronary Luminology

For more than 40 years, coronary angiography remained to be the "gold standard" for describing coronary anatomy.[1] In 1957, coronary atherosclerotic disease was first directly visualized when Sones performed the first selective coronary angiogram.[2] It marked the start of a new field of cardiovascular medicine – Interventional Cardiology. It was the beginning of a new paradigm, "Coronary Luminology", where cardiologist relied heavily on coronary angiography to guide them in their clinical practice. Unfortunately, the coronary silhouette was a relatively poor representation of the coronary anatomy which was a limited standard reference to guide them for revascularization. Angiography underestimated the severity of coronary lesion in relation to post-mortem histological findings. Later, the physiological status of the lesion was found to be poorly correlated with angiographic stenoses.[3-10]

Therefore, visual interpretation showed major discrepancies among estimations of lesion severity. Limitations of angiography had lead to inventions of better imaging of the coronary artery lumen. Intravascular ultrasonography demonstrated coronary lesions to be often complex, with markedly distorted or eccentric luminal shapes.

Then, the phenomenon of coronary "remodelling " was first described by Glagov in 1987.[11] The remodelling process was an outward displacement of the external vessel wall overlying the atheroma. This could be clearly visualized by intravascular ultrasound.

Eventually, the quantitative coronary angiography was first introduced by Brown in the late 1970's which was intended to replace the "eyeballing" evaluation of a coronary stenosis. [12] But actually, it still possessed all the shortcomings of the conventional angiogram.

Before Thrombolysis and Angioplasty in Myocardial Infarction (TAMI-1) trial was published in 1987, demonstrating that angioplasty was unnecessary and potentially

deleterious after successful thrombolysis,[13] the practice of "oculo-stenotic" reflex was common denoting the irresistible temptation among invasive cardiologists to perform angioplasty on any significant residual stenosis after thrombolysis of acute myocardial infarction.

1.2 Coronary Stenting

Thereafter, the concept, "bigger is better", was introduced.[14] This paradigm referred to the theory that a larger luminogram will translate into better clinical outcomes.[15] Afterwards, stents flourished as stimulated by greater improvement in the coronary lumen dimensions in acute and late angiographic results.[16-18] The first clinical report on coronary stenting by Sigwart indicated that metal stents produced too many thrombotic complications on cohort patient follow-up. But, they used only rudimentary antithrombotic medical regimen on their subjects.[19] Research was even directed towards optimization of stent deployment through high-pressure inflations and/ or ultrasound guidance.

1.3 High Pressure Strategy versus Arterial Injury

Colombo demonstrated that most stents deployed at 6-8 atmospheres were grossly unexpanded, asymmetrically deployed, and not apposed to the vessel wall.[20-22] Incomplete stent deployment led to mechanical flow disturbance. Together with thrombogenicity associated with arterial wall injury, inherent stent thrombogenicity primarily resulted into stent thrombosis.[23-27]

Nakamura showed that despite excellent angiographic results , most of the stents deployed at low pressure remained suboptimally expanded by IVUS criteria. But, after using high-pressure post-dilatation, stent CSA improved. Even so, the final stent CSA rarely exceeded 60-80% of the nominal balloon CSA.[20]

Colombo promoted high pressure stent implantation which was later recommended in the American College of Cardiology Expert Consensus Document on Coronary Artery Stents.[28]

High pressure inflation had been recommended in the primary percutaneous intervention of acute myocardial infarction.(≥16 atm)[29-31]

But, higher pressure strategy was equated with greater vessel wall injury. This initiated excessive tissue growth repair which translated into intimal hyperplasia and, consequently restenosis.[32-41] Several studies showed its detrimental effects on the stent and vessel. Aside from resulting in distorted stent geometry, medial injury with exposition of adventitia and lipid core penetration by struts resulted in increased inflammation.[42-45]

Farb described that after coronary stenting, early thrombus formation and acute inflammation occurred and followed by neointimal growth.[46] Thus, Farb challenged the adage, "the bigger the vessel, the better the outcome."[47] He was more inclined to preaching, "the more you gain, the more you lose."[44]

Investigators proposed an injury score for the arterial wall as a result of high pressure stent implantation on coronary lesions with correlation to higher risk of restenosis. In experimental animal studies, the extent of neointimal proliferation was associated with arterial wall damage. A lesion treated with more than 16 atmospheres and a balloon to artery ratio of more than 1.1 translated into greater angiographic late loss and lower MLD at follow-up.[17,18,48,49]

1.4 Oversizing of Stent Strategy

Johansson utilized the strategy of oversized stents to achieve optimum stent deployment but still with high inflation pressures. These improved luminal gain without having complications during routine stenting procedure. It was even associated with low target vessel revascularization.[41]

So, aside from high pressure stent implantation, interventionists tend to be more aggressive by also using oversized balloons. Goldberg found greater lumen dimensions through this approach.[50]

The CLOUT Pilot Trial declared the safe use of oversized balloons which resulted to significant luminal dimensions without increasing risks for dissection and ischemic complications.[32]

1.5 Mathemathical Modelling: Arterial Injury

Rogers used mathematical modelling through finite element analysis to understand the factors involved in vascular injury during stent implantation that lead to restenosis. Modifying the influence of these mechanical factors by optimizing stent design and stent-placement protocols could limit vascular injury and subsequently reduce restenosis. Results showed that higher inflation pressures, wider stent-strut openings, and more compliant balloon materials contributed largely to bigger surface-contact area and contact stresses between stent struts.[51]

Stent-induced arterial injury was previously considered to be limited to sites of stent struts and deep wall laceration meant greater vascular response.[44,52-54] During stent expansion, endothelial regions removed from stent struts themselves exhibit also vascular injury.[55] The balloon-artery surface stress or contact area in between stent struts with the balloon and arterial wall played a major role in vascular injury as modified by stent strut configuration, interstrut distance, placement pressure, balloon materials, and balloon compliance.[51]

Finite element analysis revealed that maximum balloon-artery surface-contact force grew in a nonlinear fashion as balloon pressure rose. A rapid increment in predicted maximum arterial-surface force between 12 and 18 atmospheres. Beyond such pressures, a plateau with the force formed. These could be applied in clinical practice wherein higher post-dilatation pressures were correlated with greater restenosis.[21,39]

1.6 Restenosis: The Most Recent Uncontrollable Dilemma

Restenosis was creating a terrible dilemma among interventionists who are currently making use of pharmacological armamentarium and newly-designed devices to prevent

revascularization. Animal studies had already documented this occurrence and was best observed in clinical investigations with the intravascular ultrasound.[35,48,56,57]

A clear understanding of the process of vascular response to stenting should be obtained to solve the problem of restenosis. Restenosis due to balloon angioplasty was caused by smooth muscle cell-rich intimal hyperplasia accompanied by arterial size and geometric remodelling changes. The inflated balloon came in contact with the normal or atherosclerotic wall surfaces, thus abrading the arterial endothelium and forming dissection planes within plaque burdens. Since the thromboresistant endothelial layer was removed, deeper wall structures were exposed to blood flow and particles. Thus, thrombosis ensued. This was just the starting phase which lead to a sequence of events including smooth muscle cell migration and proliferation, and the resulting intimal hyperplasia.[58]

The vascular response to stenting was a more extensive and prolonged course. Animal studies showed that the intimal proliferation from stenting was four times greater than balloon inflation.[59-61] Even in clinical studies, the late lumen loss was greater than balloon angioplasty.[62-65] The first phase of thrombosis occurred within the first three days after stent implantation. Platelets and fibrin were deposited on subendothelial connective tissues. Focal mural thrombus deposition occurred but did not encroach the lumen significantly. The reaction depended on how deeply the struts penetrated the wall. Greater arterial injury entailed greater thrombotic response. So, minimal arterial injury could virtually spare the involved vessel.[44,56,66] The second phase of vascular repair started at the formed thrombus in between the struts. Activated platelets released cytokines and adhesion molecules. These were the mononuclear and polymorphonuclear leukocytes that adhered to the stretched internal elastic membrane. They promoted inflammatory cell recruitment and migration across the endothelium into the arterial wall. The surface-adherent leukocytes would eventually be the determinant for the rate of proliferation within the lesion.[66] These decreased as the tissue-infiltrating macrophages increased which occurred 3-7 days after stent implantation. These cells migrated to the developing neointima to become multinucleated giant cells around struts and also to the cellular intima distant from the struts. The third phase was the intimal cell proliferation wherein inflammatory cells from the vessel surface penetrated to the

neointima seven days after stent implantation. Both smooth muscle cells and monocytes had proliferative potentials contributing to the metabolic and architectural framework of the extracellular matrix. The fourth phase involved overall deformation of the arterial wall. Elastic recoil was part of the early response. Then, geometric remodelling occurred by collagen deposition and fibrosis causing shrinkage of artery. The arterial wall squeezed through the stent strut interstices.[67] Through increased collagen deposition, marked destruction of elastin, and persistent inflammation, the artery opposed the strain forced by the stent struts. The healing process was completed by re-endothelialization occurring weeks to months. This vasculoproliferative process following stent implantation was observed both in restenosis animal models and in human atherosclerotic lesions.[45,59,68-70]Refer to Figure 1.

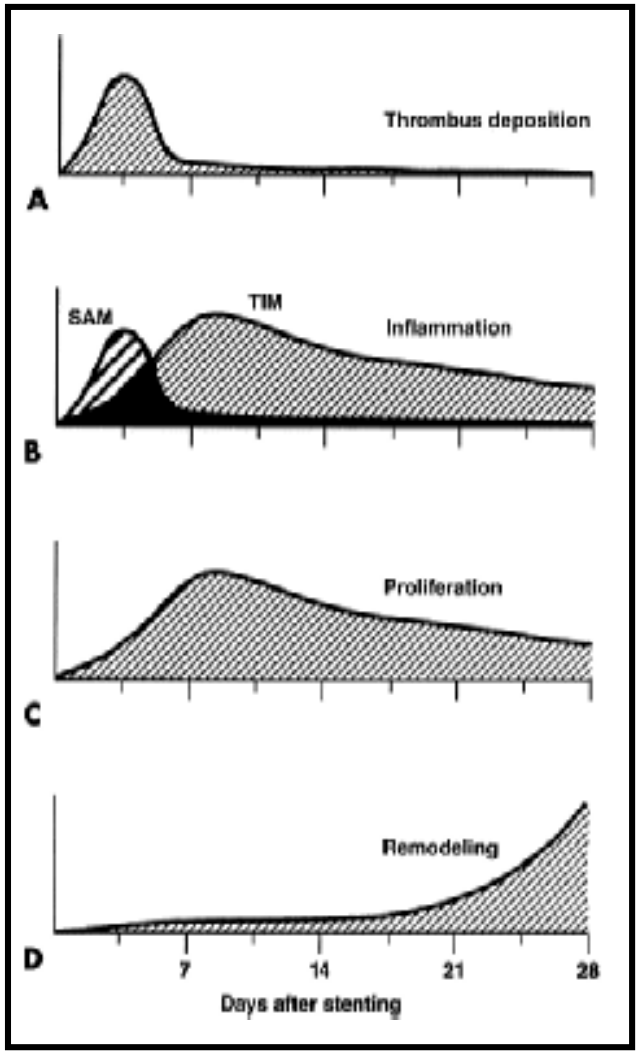

Figure 1. The graphs described the different stages of vascular repair after stent-induced arterial injury.

1.7 Statement of the Problem

New generation stents were eventually manufactured to solve the current problem of restenosis. Since restenosis was caused by arterial injury aggravated by high pressure balloon inflation, newly designed stents were continuously developed to fully expand with the use only of nominal or low pressure minimizing vessel trauma. Optimal stent deployment could only be properly monitored by QCA and IVUS. This study utilized a newly designed tubular stainless steel stent, the EXPRESS™ Coronary Stent System which was developed to adopt low pressure as its optimal deployment pressure. Therefore, the null hypothesis stated that there was no significant difference between the normal pressure stent implantation balloon inflation parameters and the high pressure postdilatation balloon inflation parameters in terms of optimal stent deployment criteria measured through QCA and IVUS making use of the new generation stent, the EXPRESS™ Coronary Stent System.

2. MATERIALS:

2.1 EXPRESS™ Coronary Stent System

This device consists of a balloon-expandable stent pre-mounted on a high-pressure delivery catheter. The stent is laser cut from 316L stainless steel tubing patterned after a specific geometric design, the TANDEM ARCHITECTURE ™ stent design. In this study, the device was intended to provide permanent structural support and to increase arterial luminal diameters in a atherosclerotic lesion of native coronary arteries by stent implantation.[71,72]

2.1.1 TANDEM ARCHITECTURE ™ Stent Design:

This stent design combines two important composite elements responsible for its first class delivery to the target lesion. Firstly, the Micro™ Elements are short, narrow radial components which contribute to its outstanding flexibility and excellent conformability in relation to the natural contour of the coronary artery. Secondly, the Macro™ Elements are composed of long, wide radial components to enhance its radiopacity and contribute to stent diameter for larger open cell area.[71]

2.1.2 Other Features:

This coronary stent system offers a lot of features to promote its first class delivery to the periphery of the coronary tree. Its Laser Bonded TrakTip™ provides precise, smooth transitions for enhanced crossability through difficult angles of atherosclerotic vessels. Crimp 360™ offers excellent stent-to-balloon securement to prevent displacement of the stent during its delivery to the target lesion. Controlled dilatation of the DYNALEAP™ balloon promotes precise stent deployment with minimal balloon overhang (no dogbone effect) and predictable balloon inflatation.[71]

3. METHODOLOGY:

3.1 Patients

3.1.1 Inclusion Criteria

Patients were decided to be included in the study only after the diagnostic coronary angiography was performed.

They were recruited in the study when they fulfilled the following criteria:

1. He presented with chronic stable angina as chief complaint.
2. His coronary angiography showed a significant de novo lesion in a native vessel or significant de novo lesions in a native vessel or vessels

A stenotic lesion was defined to be significant based on the following conditions:

1. when the stenosis diameter was more than 70% as compared to its reference diameter.
2. when the stenosis diameter was between 40 and 70% as compared to its reference diameter which was called intermediate lesion, then further evaluation by fractional flow reserve was done. When the fractional flow reserve was less than 0.75, then it was classified as significant.

When a lesion was classified to be significant, then percutaneous coronary intervention was performed.

3.1.2 Exclusion Criteria

Patients are excluded from the study when they have the following characteristics:

1. He was admitted as an emergency case.
2. The stenotic lesion was in a vein graft.

3.2 PCI Protocol

Pre-dilatations were performed once or several times at the discretion of the operator.

The stent was implanted at nominal pressure of nine atmospheres as specified by the manufacturer. A repeat coronary angiography and intravascular ultrasound were performed afterwards. When the operator perceived the stent deployment to be optimal by eyeballing based on both angiography and IVUS, then PCI has ended. The stent group was categorized as Group A.

On the other hand, when after implanting the stent at nominal pressure, the repeat angiography showed incomplete stent expansion, the operator proceeded directly to high pressure post-dilatation without performing intravascular ultrasound. The stent group was categorized as Group B.

Moreover, when the implanted stent at nominal pressure was perceived to be optimal by eye-balling based on repeat angiography, then IVUS was performed. When the stent was perceived to be optimal by eyeballing based on IVUS, then PCI has ended. The stent was categorized as Group A.

But, when the stent was perceived to be unsuccessfully deployed by eyeballing based on IVUS, the operator proceeds to high pressure post-dilatation. The stent was categorized as Group B.

Post-dilatations were performed once or several times at the discretion of the operator. See Figure 2.

3.3 Patient's Informed Consent

The study was conducted according to the Declaration of Helsinki on Biomedical Research Involving Human Subjects.[73] The study was only considered whenever the operator has chosen the EXPRESS™ Coronary Stent System to be deployed for the target lesion as determined from the diagnostic coronary angiography. Thereafter, the patient received all the necessary information before the written informed consent was obtained.

3.4 Investigator's Disclosure

This study was conducted with no vested interest for the manufacturer nor for the operators and investigator. No sponsoring was granted by the company in favor of the investigator. This study was submitted for poster presentation at the Annual Meeting of the German Cardiac Society, the European Society of Cardiology and the American College of Cardiology.

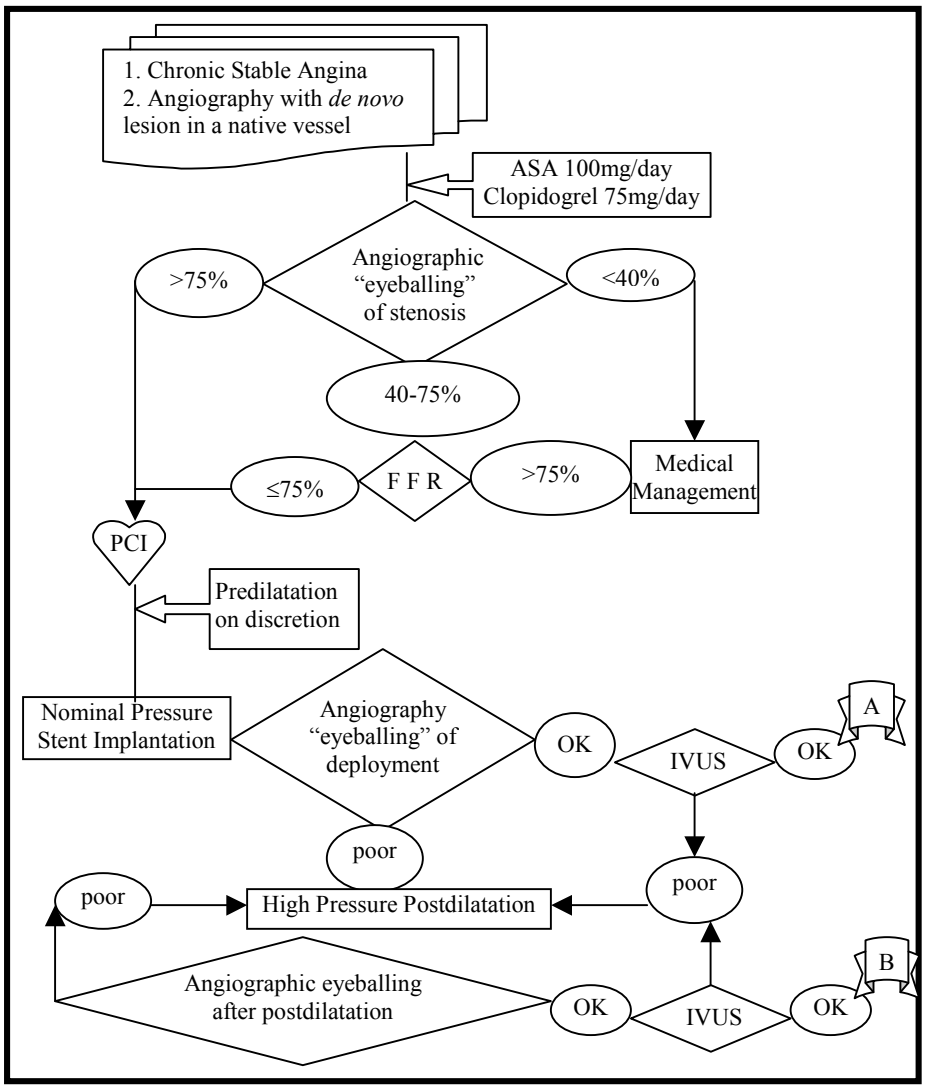

Figure 2. Algorithm of Methodology

3.5 Optimum Stent Deployment Criteria

The MUSIC criteria was used as reference for optimal stent expansion:

1. The stent must be completely apposed over the entire length against the vessel wall.
2. The minimum in-stent CSA must be ≥90% of the average reference CSA or ≥100% of the minimum reference CSA.

In case the minimum in-stent CSA reached ≥9.0mm^2,

- The minimum in-stent CSA must be ≥80% of the average reference CSA or ≥90% of the minimum reference CSA.

If the regions adjacent to the stent showed a dissection or evidence of thrombus, the operator was allowed to proceed based on his own clinical judgement, that was, to use other balloons or to insert additional stents of any type and size.

The patients with inability to evaluate the proximal or distal reference segments due to side branching were still included in the study.

3.6 Medications

3.6.1 Pre-medications:

Patients should be taking ASA at a minimum dose of 100mg per day or Clopidogrel 75mg per day. Otherwise, they were required to take Clopidogrel 75mg/tab 4 tablets as loading dose.

3.6.2 Anti-coagulation for PCI:

5,000-10,000 units of unfractionated heparin as bolus were administered intravenously after insertion of the introducer sheaths. Further boluses were given during intervention to maintain the Activated Clotting Time (ACT) to more than 250 seconds.

Intravenous unfractionated heparin boluses was no longer given after the procedure. The introducer sheaths were removed when the ACT was already below 160 seconds.

3.7 Diagnostic Modalities

3.7.1 Coronary Angiography Procedure

The Ludwig Maximilian University Hospital-Innenstadt in Munich was using INTEGRIS Allura 9 Biplane system for their catheterization laboratory. It was a biplane system for diagnostic, vascular and interventional procedures with frontal Poly DIAGNOST G-arm stand, lateral C-arc and digital imaging. Cannulation of the ostium with the appropriate diagnostic or guiding catheter was skillfully executed after sterile puncture of the femoral artery at the groin. Selective coronary angiography of the artery of interest was performed with injection of less than 10 cc of contrast medium. The coronary lesions were best visualized with proper angle projections preventing foreshortening followed by a short period of digital recording.

3.7.2 Quantitative Coronary Angiography Analysis

The new version of Cardiovascular Angiography Analysis System (CAAS II) was used to perform quantitative analysis. It was a user-friendly software allowing easy and fast analysis of cardiovascular angiographic images. These images were already digitized in the catheterization laboratory produced as Digital Imaging and Communications in Medicine, Version 3.0 (DICOM-3) image format standard and stored on the Compact Disc-Recordable (CD-R) as the exchange medium. The DICOM-3 standard prescribed that images be stored in a 512 x 512 and 1024 x 1024 bits format with 8 and 10 bits of density levels and that raw, that was, the uncompressed and unenhanced, data be made available on the DICOM-disc. Boundaries of a selected coronary segment are detected automatically. The absolute diameter (in millimeter) of the stenosis was determined using the guiding catheter as a scaling device. All study frames selected for analysis were end-diastolic to minimize motion artifacts, and arterial segments were measured between the same identifiable branch points. Refer to Figure 3.

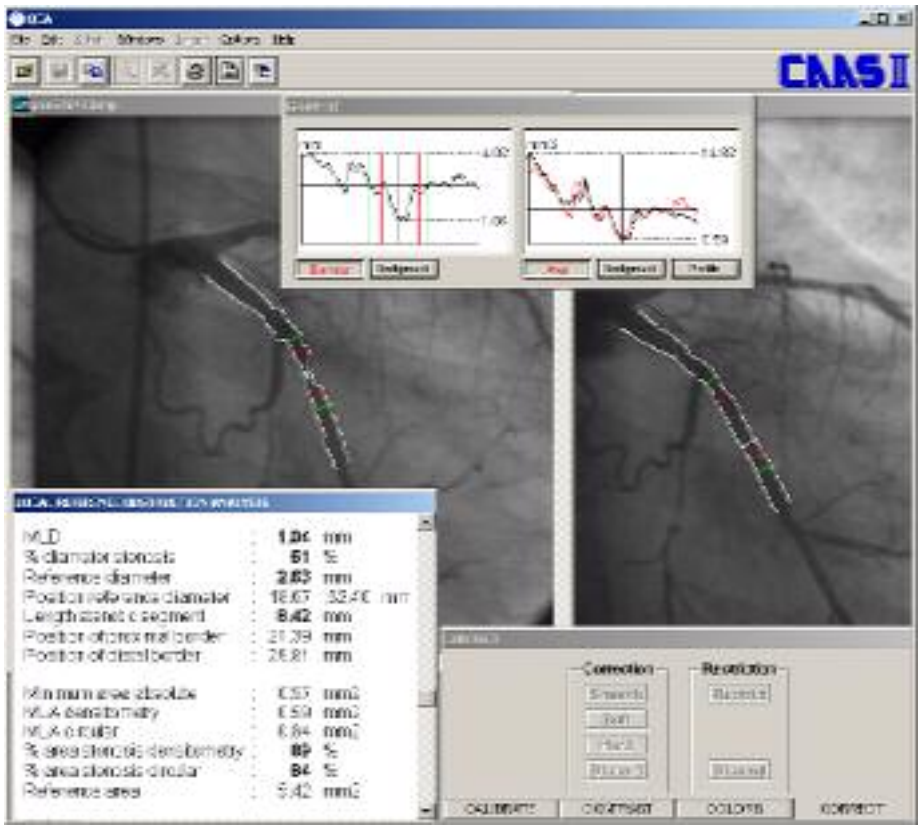

Figure 3. A sample case of QCA analysis software application wherein MLD, % diameter stenosis and the reference diameter were automatically measured after arranging the position of the lesion borders (inner lines) and reference points (outer lines). Both pre-PTCA and post-stent angiographic images were evaluated showing the automatic boundary detection. But, only the pre-PTCA results were shown.

3.7.3 Intravascular Ultrasound Examination Procedure

IVUS studies were performed with a mechanical 30 MHz imaging system. The catheter of the CVIS Insight system (Sunnyvale, CA, USA) housed an ultrasound transducer and a rotating mirror. All IVUS studies were performed after 100 to 200 µg of intracoronary nitroglycerine were administered. Care was taken to adjust the settings for time - gain compensation to yield optimal image quality. The ultrasound catheter was advanced distally over a guidewire >10 mm beyond the lesion, and an imaging run was performed to a point 10 mm proximal to the lesion with motorized transducer pullback at 0.5 mm/s. Data were recorded onto a high-resolution super-VHS videotape for offline analysis. Cross-sections of insufficient image quality to determine lumen or vessel area

and cross-sections showing a calcified lesion of >180 degrees were excluded from quantitative analysis.

3.7.4 Intravascular Ultrasound Planimetry Measurement

Quantitative IVUS analysis was performed by computerized planimetry (TapeMeasure, Indec Systems). Post-interventional stent cross-sectional areas were measured almost at 1 mm interval. The proximal and distal reference segments, the least diseased portion, were also sliced at almost 1 mm interval within 10 mm from both ends of the stent before any major side branch.. The stent struts, intima or luminal border, and external elastic membrane or media-adventitia border were distinctly identified and marked to measure the following cross-sectional areas. Refer to Figure 4 and 5.

1. Stent (luminal) area = area within the stent struts
2. Luminal area = area within the intima measured at the proximal and distal reference segments
3. Vessel area = area within the external elastic membrane
4. Lumen symmetry = ratio between minimum stent luminal diameter and maximum stent luminal diameter

Lesion calcification was also quantified using maximum arc of calcium in degrees as measure of severity. Refer to Figure 5.

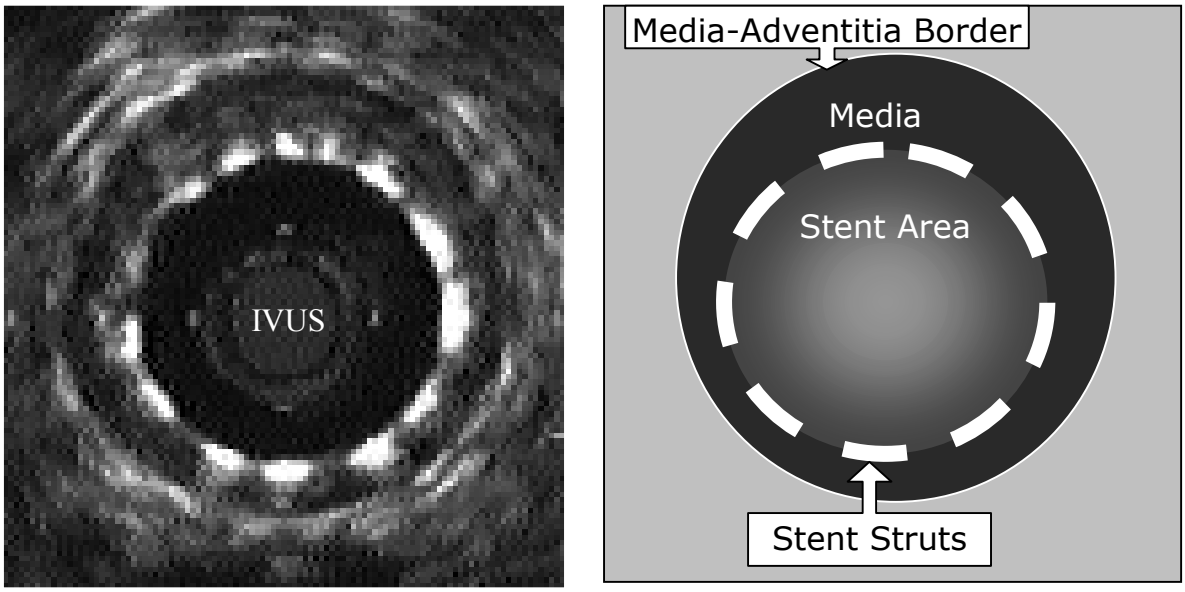

Figure 4. An IVUS image sliced within the stent segment showing fully expanded stent with good lumen symmetry and stent apposition.

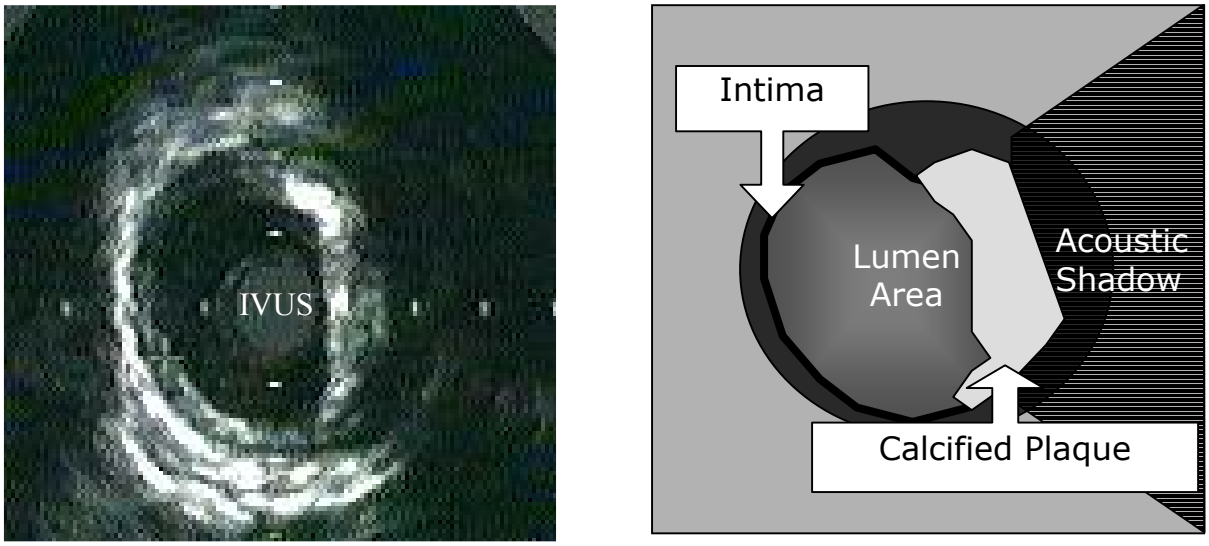

Figure 5. An IVUS image sliced at the reference segment showing irregularly shaped lumen with rough intimal border. Calcified plaque was evident due to acoustic shadowing.

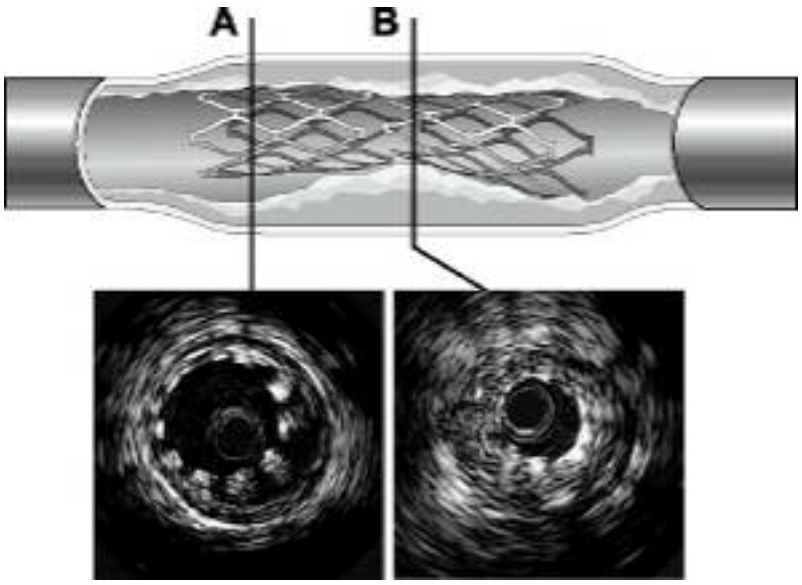

Figure 6. Demonstration of failure of stent deployment due to (A) poor apposition of stent to vessel wall and (B) underexpanded stent.

3.7.5 Myocardial Fractional Flow Reserve

Fractional flow reserve (FFR), defined as the ratio of maximum flow in the presence of a stenosis to normal maximum flow, was a lesion-specific index of stenosis severity that can be calculated by simultaneous measurement of mean arterial (P_a), and distal (P_d) coronary pressures during pharmacological vasodilation.

A 6-French guiding catheter was introduced into one femoral artery, and was advanced into the ostium of the coronary artery. P_a was monitored by this guiding catheter. Nitroglycerin 0.5 mg sublingual spray was administered and repeated every 30 minutes. Angiograms of the target vessel were then obtained as usual.

To measure P_d, an 0.018-in fiber-optic high-fidelity pressure-monitoring wire was used (Pressure-guidewire, Radi Medical Systems, Uppsala, Sweden). After calibration, this fiber-optic wire was introduced into the guiding catheter and advanced to its tip. At that point, equality of pressures registered by the guiding catheter and the fiber-optic wire was verified.

The wire was then advanced into the coronary artery and positioned across the stenosis. P_a, and P_d, were monitored continuously during the procedure. After the pressures was stabilized, maximum coronary hyperemia was obtained by intravenous adenosine (140 microgram/kg/min) infused through the side arm of the venous sheath. The further decrease of distal coronary pressure was associated with maximum hyperemia. From the simultaneous recording of P_a, and P_d at steady-state maximum hyperemia, FFR_{myo} before PTCA was automatically calculated and displayed in the RADIAnalyzer™ interface. Then manual pullback was done gradually to pinpoint the real culprit lesion. See Figure 7.

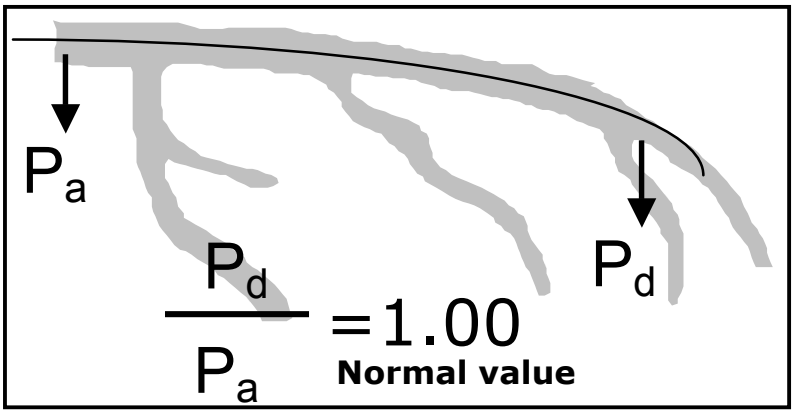

Figure 7. The FFR was calculated as a ratio of the pressure distal to the stenotic lesion or pressure of the distal part of the coronary artery as the numerator(P_d) and the aortic pressure recorded at the ostium as the denominator(P_a). [74]

The RADIAnalyzer™ interface was composed of a graphic display that presents real-time curves and numerical values. Thus, it provided hemodynamic information for use in the diagnostic and treatment of coronary artery disease.

After adenosine infusion was stopped, an adequate balloon catheter with an 0.018-in central lumen was advanced over the fiber-optic wire, and then angioplasty was performed. During the balloon inflations, P_a, and P_d (then called P_w), were also continuously recorded. After a satisfactory angiographic result was obtained, adenosine infusion was started again for post-PTCA recording of P_a, and P_d, at maximum

hyperemia. This allowed calculation of the post-PTCA value of FFR. Finally, the fiber-optic wire was withdrawn into the guiding catheter, and equality of both pressures was rechecked for drift.

Figure 8. This was the RadiAnalyzer interface showing the FFR, mean distal pressure, and mean aortic pressure. Other features of the apparatus such as the coronary flow reserve, temperature change, and transit time were shown but were not necessary for this study.

3.8 Statistics:

Due to the unequal and small sample sizes of two independent groups in the study, the necessity to check normality of distribution by Kolmogorov-Smirnov test and equality of variances by Levene test were always under consideration. After fulfilling the aforementioned required conditions, the Student's t-test for unpaired sample groups was utilized to detect differences of mean with standard deviations between groups with numerical and ordinal variables. The clinical features such as age of the patients, body mass index, serum creatinine level; angiographic measures such as minimum lumen diameter, percent diameter stenosis, reference diameter, and lesion length; and lastly, the sonographic parameters such as minimum and average cross-sectional areas of

reference and stented segments were all treated accordingly observing all required assumptions.

The chi square test was appropriate to compare proportions of nominal variables of independent groups with rather not so small frequencies. Most of the clinical profile and optimum deployment criteria by IVUS and QCA were categorical variables.

The Student's t-test for paired groups was used to compare means between stent implantation and post-dilatation cross-sectional area parameters of Group B.

Pearson's correlation coefficient *r* expressed the association of severity of calcification of lesions with the minimum and average cross-sectional area of the stent region.

4. RESULTS:

Between September 2002 and February 2004, 33 patients were enrolled in the Department of Cardiology in the University Hospital-Innenstadt of Munich.

4.1 Stent Dropouts

Out of the 47 stents used for the study, seven were excluded because of technical reasons. The seven excluded stents should have been included in Group B. Two had no angiographic film after nominal pressure stent deployment. Two had only one IVUS imaging. One was directly deployed with high pressure inflation. One IVUS examination was erased. Another IVUS examination was not possible. Therefore, only 40 stents were eligible for the study.

4.2 Patients' Profile

A total of 33 patients were enrolled in the study wherein a total of 39 lesions were treated with 40 stents.

Out of the 11 patients for Group A, two stents were implanted for each of two patients: each with two separate lesions. One had five lesions, each lesion was treated with a stent. Therefore, 11 patients received 17 stents for 17 lesions.

Of the 22 patients in Group B, only one had two stents for a long lesion. Therefore, 22 patients received 23 stents for 22 lesions.

Group B showed higher percentage of patients with hypertension, hypercholesterolemia, and higher serum creatinine level. An indication of poorer prognostic outcome for Group B but these had no clinical relevance according to statistical computations. Although Group A showed higher incidence of significant family history and history of previous myocardial infarction, it did not also reach to a significant level. See Table 1 for their clinical characteristics.

Table 1. Clinical Profile:

Characteristics of Patients (n=33)*	Group A (11)	Group B (22)
Age	63±8y/o	63±11y/o
BMI	45±5	50±8
Creatinine	1.1±0.2mg/dl	1.4±0.9mg/dl
Women	36%	23%
Smoker	41%	53%
Diabetes	29%	24%
Hypertension	65%	76%
Hypercholesterolemia	53%	65%
Family History	76%	12%
Previous MI	65%	35%
Revascularization	55%	55%

* - p-value for all parameters was not significant.

4.3 QCA Investigation

By angiographic characteristics, the lesion type according to the American Heart Association and American College of Cardiology joint classification was an important parameter dictating the outcome of percutaneous coronary intervention. Group B showed predominance of lesion type B2 while Group A showed trending towards lesion type A and B1. Therefore, Group B had poorer prognostic lesion types which later translated to clinical significance; that is, lower success rate of stent deployment. The other angiographic measures such as minimum lumen diameter, percent diameter stenosis, and lesion length had no bearing to the resulting clinical picture since they revealed no significant statistical difference. See Table 2 for their angiographic features.

Table 2. Angiographic Profile:

Characteristics of Lesions (n=39)	Nominal Pressure Stent-Implantation Group A (17)	High Pressure Post-Stent Dilatation Group B (22)	p-value
MLD (mm)	0.96±0.21	0.95±0.36	ns
Diameter Stenosis (%)	61±11	62±15	ns
Reference Diameter (mm)	2.60±0.55	2.58±0.44	ns
Lesion Length (mm)	14.45±6.49	15.39±6.23	ns
Lesion Type (ACC/AHA)			P<0.05
A	4	0	
B1	7	4	
B2	4	15	
C	2	2	
Target Vessel			-
LAD	4	3	
LCX	4	10	
RCA	9	9	

4.2 IVUS Investigation

The minimum CSA and average CSA of the reference and stented segments were comparable for both groups. The vessel CSA was also comparable according to statistical computations. The difference was certainly seen in parameters between the stent implantation and post-dilatation phases of Group B. ($p<0.05$) Therefore, the acute luminal gain was $1.29\pm0.84mm^2$ within the stented region. Refer to Table 3 for the luminal area parameters.

Table 3. IVUS Results:

CSA Parameters (mm^2)	Group A (15*)	Group B1 (20**) (Stent Implantation)	Group B2 (23) (Post-Stent Dilatation)	p-value
Min ref segment***	5.58±2.36	6.72±2.55	-	ns
Ave ref segment***	7.67±3.80	9.01±3.18	-	ns
Min in-stent	6.85±2.53	6.69±2.07	7.78±1.83	A vs B2, p=ns B1 vs B2, p<0.05
Ave in-stent	8.12±2.89	8.13±1.80	9.35±1.96	A vs B2, p=ns B1 vs B2, p<0.05
Ave vessel	17.06±6.90	17.04±4.61	17.70±4.42	A vs B2, p=ns B1 vs B2, p<0.05
Delta in-stent****	-	1.29±0.84		-
Delta vessel****	-	0.93±0.98		-

* -Two stents of Group A were implanted adjacent to another one. They were then analyzed sonographically as one stent.

** -Three stents of Group B were obviously not successfully implanted since the angiogram showed the balloons to have indentations at 9 atm. They were directly post-dilated with higher pressures without undergoing IVUS.

*** -Only the parameters at stent implantation were used throughout as reference.

**** -Additional luminal area gain noted at post-stent dilatation compared with stent implantation of group B with significantly different parameters ($p<0.05$). No pre-intervention IVUS was performed.

The description for lesion calcification was performed after intervention. Although statistics did not prove it, a trend could be delineated wherein Group B had more severe calcification as indicated by a greater arc of calcium around the stent. Even the correlation coefficients, these apparently showed negative association; that is, the heavier calcification, the smaller the stented lumen. Refer to Table 4 for further scrutiny.

Table 4. Lesion Calcification by IVUS

Entire Stented Segment	All Lesions	Group A	Group B	p-value A vs B
Maximum arc of calcium in degrees	100±65°	97±74°	102±60°	ns
Correlation with minimum CSA*	r = -0.11	r = 0.09	r = -0.34	ns
Correlation with average CSA*	r = -0.12	r = 0.07	r = -0.42	ns

*- Pearson's r correlation coefficient was used.

All coefficients were not statistically significant.

4.3 Optimum Stent Deployment Yield Analyses.

By angiographic optimum stent deployment criteria of <10%, Group A had a better yield of 53% (9/17) than stent implantation parameters of Group B, 39% (9/23). But, Group B at post-stent dilatation drastically improved to 78% (18/23). This was a clear indication of the need for higher pressure postdilatation procedure. But, aggressiveness to achieve successful stent deployment entails arterial injury. The corresponding yield by Group B of 74% (17/23) at a balloon:artery ratio of >1.0 was expected. Refer to Table 5 for the angiographic analysis.

It was the primary objective to assess by means of IVUS the optimal deployment pressure for the new generation Express™ Coronary Stent System. Based on the Modified MUSIC criteria, Group A & B had comparable success rate of 76% (13/17) and 70% (16/23), respectively. See Tables 5 for the criteria yield analysis. Please refer back to section 2.3 to review optimum stent deployment criteria.

Table 5. Yield Analyses:

Post-Interventional Analyses Total = 40 stents***		Group A (17)	Group B (23)	
			Nominal Pressure (B1)	Post-Dilatation (B2)
IVUS	a. Stent Symmetry(>0.7)*	82% (14)	91% (21)	96% (22)
	b. CSA Ratio	94% (16)	57% (13)	74% (17)
	c. Good Apposition	100%	96% (22)	100%
	Modified MUSIC Criteria**	76% (13)	48% (11)	70% (16)
QCA	<10% Diameter Stenosis	53% (9)	39% (9)	78% (18)
	Balloon:Artery >1.0	59% (10)	22% (5)	74% (17)

* -ratio of minimum stent diameter with maximum lumen diameter

** -fulfilled the three IVUS criteria as successful stent deployment

*** -p-value for all parameters were not significant
except for CSA Ratio, A vs B1, $p<0.01$

4.4 Immediate Clinical Outcome

The sonographic and angiographic criteria of optimal stent implantation were achieved in more than half of each group. No myocardial or acute coronary occlusion occurred during the procedure. No major complications such as death, emergency coronary bypass surgery or cerebro-vascular events occurred during the procedure or clinical stay.

5. DISCUSSION

5.1 Patients' Appraisal

5.1.1 Low-to-Moderate Risk Patient Selection

The patients selected for the study involved not the high-risk population. This study focused only on procedural technique that reported only immediate surrogate endpoints. Although the study mentioned also the immediate clinical outcome during the patients' hospital stay. Patients with chronic stable angina and significant de novo lesion were appropriate patients to be managed with newly designed bare stainless steel slotted tubular coronary stents.

5.1.2 Small Sample Size

Due to the small sample size of the study, only trending was appropriately used to describe the differences between the two unequal groups. The necessary robust non-parametric tests were applied only when the pre-requisites for a student's t-test were not met. Hypertension and hypercholesterolemia were major risk factors against Group B which could influence the outcome of PCI. The angiographic lesion type according to the ACC/AHA Lesion Classification System ($p<0.05$) was the break point that directly dictated the structural endpoint of PCI. From the mean parameters of IVUS, the average minimum in-stent CSA and overall in-stent CSA showed a wide margin between the two pressure groups. The lesion calcification severity measured by arc in degrees was the negative influence for Group B's intervention outcome and inversely correlated with their luminal dimensions. Describing by percentage distribution was the best option to discuss analyses of optimum stent criteria. The largest effect of high pressure technique was observed with Group B's cross-sectional area of their stent lumen. ($p<0.05$)

5.1.3 Patient's Assignment to Groups

The study utilized a stepwise procedural selection of patients for assignment of groups dependent on immediate visualized results of intervention. The patients were enrolled

consecutively who have received the EXPRESS™ Coronary Stent System as the stent used for PCI. Randomization for assignment of groups would be unethical and immoral. When patients would be assigned fixed to the nominal pressure group and their stents were only suboptimally expanded or underexpanded, these subset of patients would be predisposed to subacute thrombosis.[23-27]

5.1.4 High Pressure Post-dilatation Group as Control

Since the study was started at that time when the high pressure strategy was already recommended by the American College of Cardiology Expert Consensus Document on Coronary Artery Stents, the high pressure group would be appropriately assigned as the control group. The new generation Express coronary stent system was believed to be recently developed to employ only nominal pressure enough to optimally expand the stent into a coronary lesion. Newly designed stents were still being developed since the recommended high pressure technique was believed to create more arterial injury that would translate to greater restenosis.[32-44] Once the MUSIC criteria had been met, the stent was classified as "successfully deployed" even though post-dilatation procedure could enlarge further the stent lumen area. The policy "the bigger, the better" was not carried out as a protocol in this study.[14,15]

5.1.5 Low or Nominal Balloon Inflation Pressure Proponents

Di Mario mentioned that high pressure strategy was already obsolete and unnecessary with the modern pre-mounted second and third generation stents.[32] These newly-designed stents were mechanically crimped on dedicated balloons and could be evenly expanded at low pressures. On the other hand, they had to overcome the resistance to expansion of severe calcified plaques. But the CONSERVE trial did not prove that newly designed stents like the LP stent can be fully expanded by low inflation pressure.[76] Takano's study also revealed that the mean minimum stent CSA of 38 new generation stents in 32 patients achieved only 62% of the manufacturer's expected stent area despite moderately high-pressure inflations of 14-16 atm.[77]

But, an exceptionally good long-term clinical outcome defined by a low rate of clinical events supports the theory that low restenosis rate and secondary good long-term clinical outcome could be achieved when adequate stent deployment was effected by the use of low pressure inflation. This was supported by several studies including that of Cafri.[37,38,78,79] 61% of stented lesions fulfilled the IVUS criteria of appropriate stent deployment using only low inflation pressure of 10 atmospheres was seen in Hoffmann's study.[80]

5.2 Procedural Appraisal

5.2.1 Exactness of Inflation Pressure Range

A clear-cut definition of high pressure should be described. The American College of Cardiology Expert Consensus Document on Coronary Artery Stents recommended ≥12-16 atm to be used as high-pressure inflation.[28] This was the pressure range used also by the proponents.[20,21]

In our study, there were deviations from the pre-defined pressure range in both groups. A cross-over of individualized inflation pressures probably indicated that a standard protocol can not be applied to all kinds of lesions. Dirschinger also deviated from the study protocol to individualize lesion management.[81]

Other studies used higher pressure of ≥16 atm.[82-87] Schatz tried to define the low pressure range using 6-10 atm[23] or 9-12 atm.[88] Before the advent of the high-pressure technique, the BENESTENT trial used a mean of 10±8 atm.[89] Several studies support that low-pressure deployment as low as less than 9 atm is associated with higher rate of adverse events. Cafri used an average inflation pressure of 8.0 atm which was associated with higher frequency of stent thrombosis (6.6%) with subsequent adverse clinical events despite the routine utilization of ticlopidine –aspirin treatment.[78] Similar rates of stent thrombosis were observed by Karrillon who used less than 8 atm showing 4.9% incidence.[90] Goldberg reported 4.4% event rate using 9 atm.[91] Sick, in his recent comparative analysis of AVE microstents with low and high pressure approach, showed higher sub-acute thrombosis rate in a group with mean pressure of 8.8 atm.[92] Therefore, a low inflation pressure for stent implantation should not be routinely used. Sometimes

neointimal proliferation was not related to stent implantation aggressiveness, rather it was directly related to plaque lesion characteristics dictating modifications in stent implantation pressures. This was supported by studies giving importance to lesion plaque burden as a predictor for subsequent tissue proliferation with greater lesion plaque burden requiring greater stent implantation forces.

5.2.2 Diversified Interpretation of Optimization of Stent Deployment

Hanekamp used also myocardial fractional flow reserve as one of the modalities to evaluate optimum stent deployment as compared with other evaluation modalities. A graph showed the cumulative distribution of observations with optimum stent deployment according to different evaluation modalities in relation to increasing inflation pressure. For the Wiktor-I stent in the study, the inflation pressures necessary to obtain optimum stent deployment as assessed by IVUS are higher than the equivalent pressures needed as assessed by QCA alone. During the step-up of pressures, a total of 81 paired IVUS and FFR measurements were performed, of which 91% yielded concordant results. Optimum stent deployment according to IVUS or FFR was always achieved only in 60% of cases. Refer to Figure 9.[93]

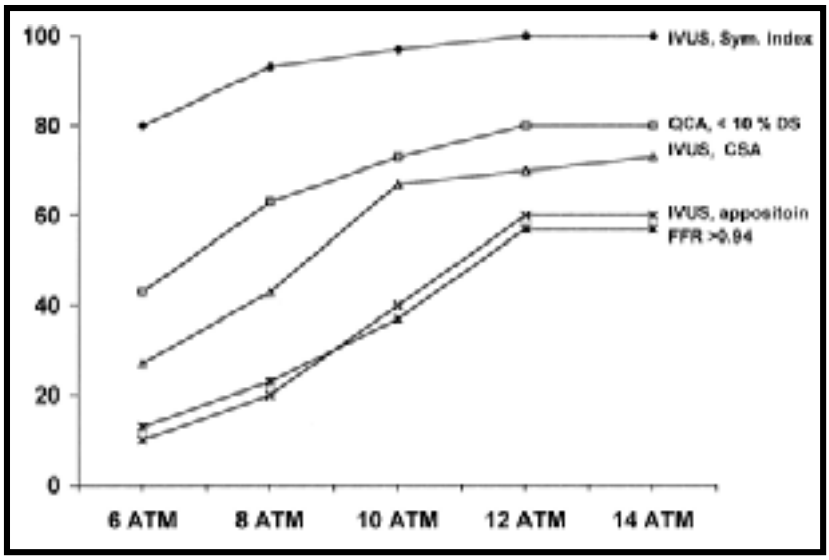

Figure 9. Graph depicted that even with high pressure strategy, only 60% of the patients could achieve optimum stent deployment based on IVUS and FFR.

Moussa maximized the use of IVUS in determining the optimum deployment criteria. Out of five IVUS criteria, the protocol with 55% ratio between in-stent mimimal lumen CSA and average reference vessel CSA showed the lowest incidence of restenosis. He emphasized that IVUS was the best guide to stent implantation. Useful information provided by IVUS to be considered by the operator were appropriate balloon upsizing, and the media-to-media diameter for target lumen gain.[50]

The modified MUSIC criteria for optimum stent deployment should be observed during PCI since it had reported to have the lowest restenosis rate of 10%. Refer to Figure 10. Both two groups met the criteria similar to the MUSIC trial of 81%.[94,95]

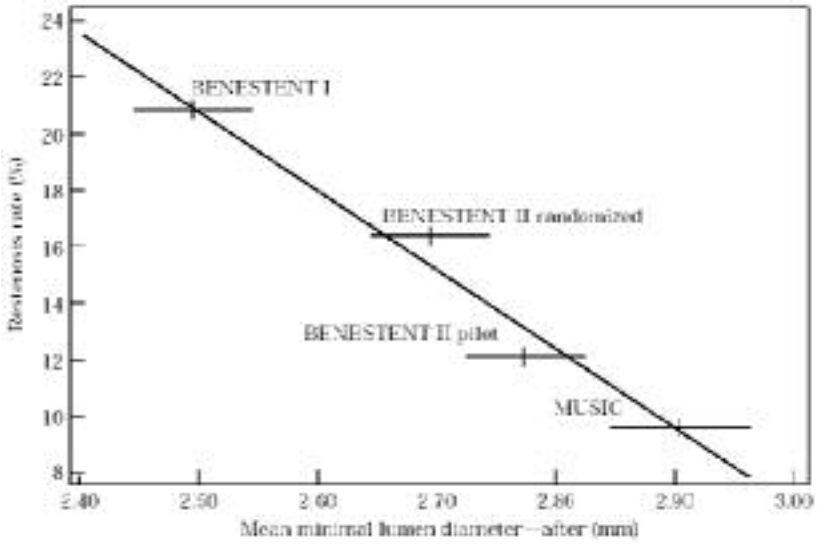

Figure 10. The linear curve revealed that the average MLD was inversely related to restenosis rate. The MUSIC trial was effective in obtaining larger luminal dimensions translating to better long-term outcome.

5.2.3 Effect of Pre-Dilatation

Stent implantation preceded by predilatation already meant almost 100% circumferential endothelial denudation. But, partial retention of endothelium in case of primary stent implantation was associated with reduced mural thrombosis, inflammation and subsequent neointimal hyperplasia. So, Hoffman's study on different deployment pressures might had obscured the results for stent-induced vascular injury due to pre-

dilatation of the lesion.[70,96] Similar consequence should also be considered in our study since majority of our patients were pre-dilated prior to stenting.

5. 2.4 Improvement in Stent Designs

For tubular-slotted designed stents such as Palmaz-Schatz stents, high-pressure adjunctive balloon dilatation at 16 atm or higher pressures became a routine practice. The Palmaz-Schatz stents showed complete stent expansion and apposition to the vessel wall minimizing thrombogenicity without using systemic anticoagulation.[57,64,97] Dirschinger used slotted-tube stents of five different types and showed more favourable acute angiographic results at 30-days follow-up from high-pressure implantation.[81]

High-pressure balloon dilatation seemed necessary for first-generation balloon expandable stents due to their design limitations.[21,57] These design limitations included reduced axial flexibility (slotted tubular design), poor trackability through tortuous anatomy, inadequate scaffoldings (coiled designs), limited size range (lengths and diameters), and suboptimal radiopacity. To compensate for these shortcomings, modifications in the material, geometry, and surface coverage of stents were incorporated into the second-generation stents, which provided high radial strength, excellent longitudinal flexibility, and better vessel scaffolding. But, inspite of these, most stents still had low yield for optimum deployment due to the semi-compliant balloon material of the stent delivery system.[98]

Caixeta tried another stent design using MultiLink Stents for implantation pressure comparison. These were balloon expandable stainless-steel stent with interconnected corrugated rings structure model. At first, it was not advised to dilate it with high pressure because it could be deformed without really offering any clinical benefits or exhibiting better luminal dimensions than nominal pressures.[99-101] Kalmar used the same stent between 9 and 15 atm since beyond 15 atm, very minimal lumen gain was attained.[48]

The Austrian Wiktor Stent Study Group utilized their uniquely designed stent, a single-wire tantalum coil stent, for conventional low pressure deployment and high pressure

post-dilatation. Their study demonstrated favourable short- and long-term results with a trend towards additional lumen gain by high-pressure post-dilatation. But, this did not translate into measurable improvement in long-term outcome.[102]

On the other hand, Caixeta demonstrated a greater acute gain with high pressure strategy. This was supported by other reports based on QCA and IVUS, even with favourable early clinical outcome.[101,103-105]

The new generation EXPRESS™ Coronary Stent System was recently developed to solve the problem of acute vascular injury aggravated by high pressure technique. This was a slotted tubular stainless steel with a new geometric mesh design. It had Tandem Architecture™ technology, which had combined Micro and Macro elements for a high degree of vessel support, and consistent radial strength.[71] See Figure 11.

Figure 11. This stent design demonstrated the Tandem Architecture™ technology.

Recently, the same stent was developed into Taxus, a slow-release, polymer-based, paclitaxel-eluting stent to reduce the risk of restenosis after the treatment of short, focal atherosclerotic lesions in humans. Paclitaxel is a lipophilic substance that came from the Pacific yew tree *Taxus brevifolia* and inhibited cellular processes of reproduction, motility, activation, secretory processes, and signal transduction. In vitro and in vivo studies demonstrated its effectiveness in reducing neointimal hyperplasia after balloon-

and stent-mediated injury. It became a slow-release, polymer-based, paclitaxel-eluting stent to reduce the risk of restenosis after the treatment of short, focal atherosclerotic lesions in humans had been demonstrated in small-to-moderate-sized studies.[106]

5.2.5 Improvement in Balloon Material

Improvement of balloon characteristics encouraged the use of high pressure. Modern balloons with pre-mounted stents had a rated burst pressure of at least 14-18 atmospheres and grow predictably when high inflation pressures were used. Focal balloon technology, precise matching of balloon and stent length with very short balloon shoulders, balloon materials ensuring low predictable compliances, and evenly distributed diameter changes along the balloon length (no dog-bone effect) had made high-pressure stent implantation a technique easier to apply and less prone to procedural complications.[32]

The opposing effect of high pressure strategy between large post-procedural luminal dimensions and subsequent arterial injury might be resolved by the use of less compliant balloons to release consistent high pressure on the stent struts without increased balloon to artery surface contact stress during implantation.[107]

The early-generation balloon-expandable stents used for PCI were delivered with compliant balloons that required postdilatation with noncompliant balloons at high pressure to optimize stent deployment.[21,94,98,108] In the Angiography Versus Intravascular Ultrasound-Directed Stent Placement (AVID) Study, 57% of patients achieved optimum stent deployment criteria after postdilatation with high pressure balloons.[109] IVUS-guided, high-pressure balloon inflations provided larger minimal stent area which translated into better long-term outcome.[64,98]

But, Roberts proved that the non-compliant nature of balloons for postdilatation which were of the same size and inflated to the same pressure as the current semi-compliant stent deployment balloons was responsible for stent expansion.[110]

There was no uniform balloon used in our study for post-dilatation procedure which could had worsened the real effects of high pressure stent deployment.

But, the EXPRESS™ Coronary Stent System used the DynaLeap™ balloon material which was characterized by minimal overhang and predictable and controlled balloon growth sizing. These features promoted precise stent dilatation and offered the right combination of softness and low profile.[71] See Figure 12.

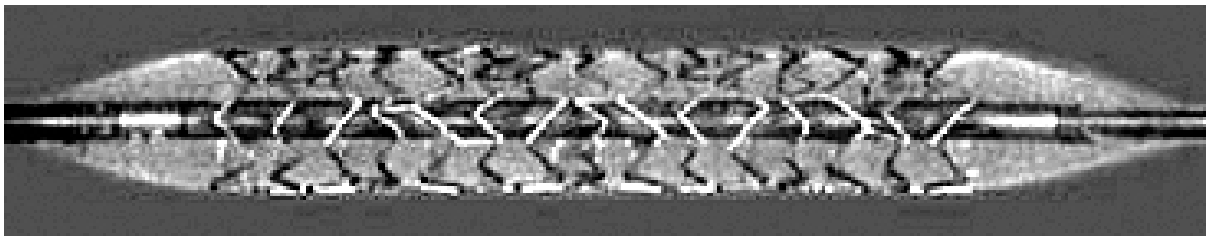

Figure 12. This special balloon material, DynaLeap™, was semi-compliant but displayed predictable and controlled balloon dilatation

5.2.6 Anti-thrombotics and anti-coagulants

The high-pressure strategy coincided with the emergence of ticlopidine plus aspirin as a post-stenting therapy. The advantage of combined anti-platelet therapy over anticoagulation for the prevention of stent thrombosis might had boost the positive effect of high-pressure technique on restenosis. Since it also improved flow characteristics, the independent role of Colombo's idea should be clarified.[82,111-115]

Dirschinger showed no significant difference between the low and high pressure groups in terms of complications.[81] Mattos showed also no improvement in late outcome.[116] The reported range of stent thrombosis was similar for patients treated with combined anti-platelet agents after stenting.[21,22,90,117]

Anti-thrombotic regimen was still maintained on all our patients after PCI.

5.2.7 Comparison with Other Studies

Hoffman used similar low to moderate risk subset (symptomatic one-vessel coronary artery disease) but with a bigger population (120) using also a new generation stent, Multi-Link HP stent. Randomization was performed after which they described separately that subset from the low pressure group that required additional postdilatations. Low pressure stent implantation was found to be inadequate even with the new generation stent. High-pressure technique did not cause more significant neointimal proliferation and the resulting larger luminal parameters were maintained on follow-up.[47]

Dirschinger excluded also high-risk patients in their study using various stainless steel stents with new multicellular designs. A successful stent deployment only defined angiographically as a diameter stenosis of less than 30% was a very lenient rule. Thirty-day and one-year outcome assessments were included in their protocol. One –year outcome did not show any advantage of high-pressure strategy.[81]

Cafri's retrospective study of 90 consecutive patients using AVE microstent used only low pressure inflation. Oversizing of stent or balloon was utilized obtaining a vessel ratio of 1:1. No control group (high pressure) was included for comparison. Again, the angiographic success was defined loosely at less than 30% diameter stenosis. No IVUS was used. Complete stent expansion on both pressure strategies indicated long term benefits, together with aggressive anti-platelet regimens. But, low pressure technique should be selectively performed deriving also benefits from lesser degree of vessel trauma.[78]

Caixeta's study indicated consecutive collection of patients with the first half having low pressure balloon inflation (<16 atm) and then the second half having high pressure technique. (>16 atm) Multilink stents were used observing only angiographic and clinical outcome until six-months follow-up. No randomization was done. The patient with transmural myocardial infarction was excluded from the study. They only counted in all successful cases for evaluation. Only a trend was seen at six-month follow-up wherein the high pressure group had lower restenosis.[49]

The Austrian Wiktor stent study group conducted a prospective randomized multicenter trial using QCA and IVUS to describe result parameters. No criteria was observed for optimum stent deployment. Short and long term outcome were gauged through loss indices of restenosis and clinical hard endpoints. No difference in outcome was seen between the two groups. But, low incidence of adverse events and target lesion restenosis were observed with the use of single-strand helical coiled tantalum Wiktor stent.[118]

Görge characterized the differences in IVUS between the two pressure groups using Palmaz-Schatz stents. This was not randomized and was performed as an emergency procedure. The IVUS criteria for successful deployment used stent symmetry, MLD, stent apposition with luminal wall and absence of residual dissection as parameters. Optimal stent expansion was not observed in all patients with high pressure strategy.[57]

5.3 Results' Appraisal

5.3.1 Effect of Lesion Calcification on Stenting

The high pressure group was also evaluated by QCA and IVUS during the nominal pressure stent implantation phase for intra-group comparison of parameters. An important observation in this study was the subset of patients with stents not fully expanded during the nominal pressure stent implantation phase remained suboptimally expanded even on repeated high pressure post-dilatation. Further scrutiny of these patients revealed that they had the worst lesion types, together with heavy calcification.

Vavuranakis demonstrated that the calcium factor in atherosclerotic plaques could not be completely eliminated by high pressure strategy. Increase in stent lumen area was achieved with this technique in moderate to severely calcified lesions but with poor lumen symmetry which was probably due to vessel overexpansion at the non-calcified segments.[119]

5.3.2 Balloon Sub-expansion and Acute Elastic Recoil

Aside from calcification as the probable cause, Bermejo elaborated also on two other possible mechanisms of residual lumen stenosis: balloon subexpansion and elastic recoil. Balloon sub-expansion was defined angiographically by the ratio of minimum balloon diameter with maximum balloon diameter.[120]

Balloon sub-expansion could result from interference of stent architecture. A study showed that Palmaz-Schatz stents expand by almost 90% reaching 5 atmospheres. Beyond this limit, it was believed that no significant increase in pressure would be able to fully expand this balloon-stent assembly.[121] Greater compliance of balloons could also be partly responsible for such defect. This was clearly observed with the Wiktor stents after implantation.[120]

Immediate reduction of the vessel lumen sometimes occurred immediately after balloon deflation accounting for approximately 50% loss in acute lumen gain during PTCA. This was called acute elastic recoil.[122-124] With the use of stents, recoil had narrowed only the lumen CSA to 20%.[119] Studies of Wiktor and Palmaz-Schatz stents showed 12% loss angiographically.[62,63,125-130]Another mechanism of lumen recoil was plaque protrusion through the stent struts because of its small metallic surface. This could be easily seen by IVUS and angioscopy.[131-133]

Carrozza showed that the acute elastic recoil was greater for coiled stents (30%) while that of slotted-tube stents is only half.(15-17%) The effect of acute elastic recoil was clearly demonstrated in this animal study with the use of a special IVUS imaging core inserted within the inflated balloon. This finding was also observed by Bermejo[120] and Werner[133]. Therefore, to achieve a final stent-to-artery ratio of 1.0, the coiled stents would need to be over-expanded to a balloon-to-artery area ratio of 1.4 (diameter ratio of 1.2), whereas slotted-tube stents should had an area ratio of 1.2 (diameter ratio of 1.1).[134]

Improvement of balloon-vessel matching might reduce residual lumen stenosis after stenting. This could be possible only with the use of IVUS as can be seen from the good

results of standard PTCA procedure.[135] The plaque responsible for subexpansion and recoil was best illustrated by IVUS.[136] Therefore, a customized deployment technique could be performed.

Another way of increasing luminal dimensions was by debulking before stenting because it modified vessel impedance.[136-138]

5.3.3 Deviation from Expected Outcome

The angiographic and sonographic results in the high pressure group after post-dilatation were as expected which were within the range of successful deployment percentage of 60-80%.[20]

But, the sonographic results of Group A were higher than expected since only nominal pressure was used. The only possible mechanisms that could lead to such good surrogate endpoints was the characteristics of the patients in Group A. Their clinical profile indicated mild to moderate risk for acute coronary syndrome. The prominent milder angiographic lesion type ($p<0.05$) including also milder lesion calcification severity by measure of circumferential calcium could have brought about the favourable outcome of PCI.

5.3.4 Discrepancy Between Two Imaging Modalities

Another point of argument was the discrepancy between angiographic and sonographic yield of optimum stent deployment criteria. Blasini compared both imaging modalities in relation to varying dilation pressures. Findings showed that on low pressure dilation, relying solely on intra-stent MLD by QCA will not yield accurate information. But, after high pressure dilation, the difference between IVUS and QCA was minimized. The possible explanation was that IVUS can detect the contact of the nearly radiolucent but highly echographic struts with the vessel wall and their shape as the endoluminal outline. On the other hand, the outline of the vessel wall between the stent struts consisted the demarcation line for endoluminal diameter. In other words, the QCA

detected only the irregularly shaped plaque formation to determine intra-stent MLD.[139,140]

5.3.5 Definition of Structural Ratios Affecting Vessel Injury

In this study, only the balloon:artery ratio was defined angiographically to depict acute injury score. But, other investigators had their own preference to relate to injury. Carroza used a special imaging core wire entered through the guide wire lumen of the balloon catheter to measure the actual balloon dilatation. Thus, a more accurate measurement of balloon:artery ratio was achieved. Another group has simply used the manufacturer's product specification to define stent:artery ratio.[134]

5.4 Limitations of the study

Since the study was conducted on a stepwise procedure with assignment to groups depending on the initial deployment outcome, randomization of patients to assigned groups would had removed selection biases. On ethical grounds, additional dilatation to the nominal pressure group should be performed on inadequately expanded stents, they then belong to a special subset of the nominal group requiring a separate scrutiny.

Like the study of Blasini, IVUS was performed only after stent deployment. Thus, the IVUS assessment of plaque burden and morphology was limited due to the metallic stent struts covering the plaque region. A detailed qualitative plaque analysis was not possible. The impact of plaque morphology on stent expansion was inconclusive.[139] But, superficial assessment of severity of calcification was possibly measured by degrees in circumferential arc since the EXPRESS™ Coronary Stent System allowed clear visualization of structures behind the struts despite its echogenicity.

The study dealt only with immediate procedural outcome of PCI with particular emphasis on compliance to optimum stent deployment criteria based on IVUS and QCA. Results would be more dramatic when in-stent restenoses could be monitored on a six-months follow-up. Furthermore, long-term clinical hard endpoints such as

mortality and clinical vascular events could also be reported to correlate with procedural objectives.

Small sample size could have affected the true outcome of the study. Trending was the only alternative to describe results whenever statistical tools utilized did not provide adequate level of significance.

5.5 Summary of Discussion

Because of the deleterious vascular injury and resulting restenosis from high pressure post-dilatation strategy, the EXPRESS™ Coronary Stent System was recently developed with its new features: the Tandem Architecture™ technological design and DynaLeap™ balloon material. With its new characteristics, nominal pressure was supposed to be enough to achieve optimum stent implantation. The high pressure post-dilatation group became the control group. The modified MUSIC criteria was used because its yield translates into 10% restenosis. Unfortunately, this study examined only immediate procedural outcome. Most studies observed also short and long-term outcomes. Assignment of patients to groups was dependent on procedural outcome and operator's discretion. Since randomization was not carried out, the high pressure post-dilatation group had poorer prognostic outcome due to its worse AHA/ACC lesion type ($p<0.05$) and tendency to have more severe lesion calcification. Due to its small sample size of low-to-moderate risk patients, trending could only be described from most of the results. As seen in other investigations, a few cross-over of pressure ranges was carried out due the operator's discretion applying the appropriate pressure for different sorts of lesions. Discrepancy in interpretation between QCA and IVUS was observed resulting from inaccuracies in the automatic border detection of the QCA software after low pressure stent implantation. Several studies showed also similar QCA and IVUS yield of optimized criteria of 60-80% including the discrepancy in their interpretations. Calcification, balloon sub-expansion and acute elastic recoil were the possible mechanisms responsible for failed stent deployment. Pre-dilatation meant almost complete circumferential endothelial denudation which might had distorted out results. Anti-thrombotics and anti-coagulants should always complement the stenting procedure.

6. CONCLUSION

Based on QCA and IVUS optimum stent deployment criteria, the nominal pressure stent implantation parameters of Group A were comparable with the high pressure post-dilatation parameters of Group B. But, the non-randomized procedural outcome assignment protocol of patients probably predisposed Group B to poorer prognosis due to its worse AHA/ACC lesion type and tendency to heavier lesion calcification. The inaccurate automatic vessel border detection may have obscured the nominal pressure results leading to discrepancies between the two imaging modalities.

7. SUMMARY

Despite being recommended by the American College of Cardiology Expert Consensus Document on Coronary Artery Stents, high pressure post-dilatation strategy still encountered several controversies due to its deleterious effects on the vascular wall and its distortion of the stent geometry leading to a predilection to restenosis. Researches were geared to the development of newly designed coronary stent systems to be deployed at low pressure minimizing vessel trauma. In this study, the EXPRESS™ Coronary Stent System underwent scrutiny based on QCA and IVUS comparing both nominal and high balloon inflation pressures.

IVUS and selective coronary angiography were performed after initial stent deployment at 9 atmospheres and after post-stent dilatation up to as high as 20 atmospheres. If stent deployment was not perceived to be optimal, stent was dilated once to three times and post-stent balloon inflation pressure could be increased at the discretion of the investigator until perceived to be optimally expanded according to the Modified "MUSIC" criteria.

Stents implanted at nominal pressure and perceived to be already successfully deployed sonographically and angiographically belonged to Group A (n=17). No high-pressure post-stent dilatation was required.

Stents implanted at nominal pressure and perceived to be not optimal by angiography with or without IVUS were further dilated with higher balloon pressure inflations until perceived to be successfully deployed based on angiography and IVUS. These belonged to Group B (n=23).

Pre-dilatation was performed on both groups once to three times when perceived to be necessary. The routine protocol for anti-thrombotics and anti-coagulants was also followed.

The immediate outcome of PCI from both groups were comparable. However, the high pressure group had poorer AHA/ACC lesion type and heavier lesion calcification. This could had prevented achieving a much higher yield of successful stent deployment. The inaccurate QCA interpretation at low pressures could have explained the apparent disagreement between the two imaging modalities.

8. ZUSAMMENFASSUNG

Obwohl die Dilatation unter Hochdruck durch die American College of Cardiology Expert Consensus Document on Coronary Artery Stents empfohlen wird, gibt es noch einige Kontroversen bezüglich der möglicherweisen schädigenden Effekte auf die Gefäßwand sowie die Verzerrung der Stentgeometrie. Beides führt zu einem erhöhten Restenoserisiko. Um eben dieses Risiko zu minimieren, werden derzeit Niederdrucksysteme erforscht. In der vorliegenden Studie wurde das EXPRESS™ Coronary Stent System unter nominaler und hoher Balloninflatation mittels QCA und IVUS verglichen. QCA wurden nach Stentexpansion zunächst bis 9 atm sowie Hochdruckdilatation bis zu 20 atm durchgeführt. Wenn die Stentexpansion dabei nicht optimal war, konnte der Stent ein- bis dreimal erweitert werden und der Balloninflatationsdruck nach Einchätzung des durchführenden Arztes (Katheteriseurs) erhöht werden, um entsprechend den modifizierten „MUSIC“ kriterien optimiert zu werden.

Stents, die nach IVUS and QCA Beurteilung bereits mit nominalem Druck optimal implantiert waren, gehöhrten der Gruppe A (n=17) an. Eine Hochdruckdilatation nach Dehnung war hier nicht erforderlich.

Stents, die mit nominalem Druck implantiert wurden und nach IVUS bzw. QCA-Kontrolle nicht optimal waren, wurden noch einmal mit Hochdruckinflatation entfaltet bis das Ergebnis basierend auf IVUS und QCA optimal war (Gruppe B, u = 23).

Eine Prädilatation wurde an beiden Gruppen ein- bis zu dreimal durchgeführt, je nach Notwendigkeit. Das Routineprotokoll für antithrombotische und antikoagulatorische Medikation wurde eingehalten. Das sofortige Resultat von PCI war bei beiden Gruppen ähnlich. Die Hochdruckgruppe zeigte jedoch schlechtere Koronarläsiontypen nach AHA/ACC und schwere Gefäßkalkbildung. Dies könnte ein Grund für die niedrigere Anzahl erfolgreicher Stentexpansionen sein. Die ungenaue QCA Interpretation bei Niedrigdruckdilatation könnte die schlechte Korrelation zwischen QCA und IVUS erklären.

9. APPENDICES

Appendix A. Classification of Lesion Type

Lesion Classification According to Standard American Heart Association/ American College of Cardiology Grading System
Type A
Discrete
Concentric
Readily accessible
Non-angulated segment
Smooth contour
Little or no calcification
Non-ostial
No major side branch involved
Absence of thrombus
Type B
Tubular
Eccentric
Moderate tortuosity
Moderately angulated segment (45°–90°)
Irregular contour
Moderate-heavy calcification
Total occlusion, 3 months duration
Ostial in location
Bifurcation lesion
Some thrombus present
Type C
Diffuse
Excessive tortuosity
Extremely angulated segment
Total occlusion, 3 months duration
Inability to protect major side branch
Degenerated vein graft lesion
B1 lesions consist of 1 B characteristic and B2 lesions consist of ≥2 B characteristics.

Appendix B. Classification of Angina

Grading of Angina Pectoris by the Canadian Cardiovascular Society Classification System
Class I
Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina occurs with strenuous, rapid or prolonged exertion at work or recreation.
Class II
Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.
Class III
Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal condition and at a normal pace.
Class IV
Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest.

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